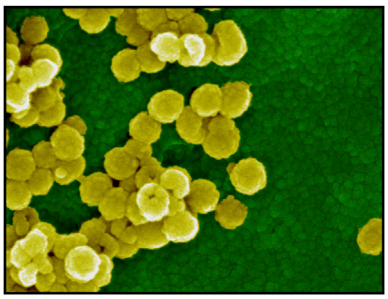
Cell

Opening the HIV Mystery Box

Nearly 36 million people live with the human immunodeficiency virus (HIV). Despite incredible advances in combined antiretroviral therapy, the hopes for a definitive cure and an effective vaccine have been frustrated by the seemingly endless capacity of the virus to subvert the host defenses, to persist in a latent state, and to resist drug interventions. Recent work, however, sheds new light on the pathogenesis of infection and unveils new tools to combat the ultimate enemy—the latent virus.



HIV-1 particles assembling at the surface of an infected cell. Image courtesy of Paul Bieniasz.

HIV Crosses the Monkey Barrier

Viral adaptation to a new host requires overcoming natural barriers to infection presented by host restriction factors. The HIV exhibits very narrow tropism, which reduces the risk of zoonoses but also limits the use of animal models to study the dynamics of infection and the development of acquired immunodeficiency syndrome (AIDS). Paul Bieniasz and colleagues now show that it is possible to adapt HIV-1 to productively infect and cause AIDS in monkeys. The trick is to infect pigtailed macaques that naturally lack the HIV-restricting protein TRIM5 with an HIV strain encoding the simian immunodeficiency virus Vif to antagonize several macaque proteins that would otherwise restrict HIV-1 infection. These measures, accompanied by transient CD8 T cell depletion to alleviate the immune pressure and increase initial viral population size, allow for the replication and successful infection of the new host. The resulting adapted virus is capable of causing an immunodeficiency syndrome that reproduces the key features of the disease in humans, providing a new animal model to dissect the pathogenesis of HIV infection. Importantly, only $CD8^+$ T-cell-depleted monkeys progress with immunodeficiency, whereas animals with intact $CD8^+$ T cell populations seroconvert and control the infection. Immune insult during the primary phase of the infection may thus be a major contributor to the clinical outcome of the disease.

Hatziioannou, T., et al. (2014). Science 344, 1401–1405.

Baby Antibodies Broadly Neutralize

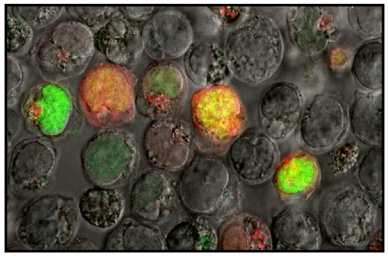
Only a subset of adults infected with HIV-1 develop broadly neutralizing antibodies (bNAbs), which are thought to take years to develop because of the need to accumulate an unusually high number of somatic hypermutations. To require the needed breadth entails repeated cycles of maturation in the germinal centers. A recent report from Julie Overbaugh and colleagues challenges this notion by showing that bNAbs quickly develop in infants exposed to HIV infection in utero. These antibodies are not due to passive transfer of maternal antibodies through the placenta and represent de novo generation of antibodies by the infants B cells. In many cases, a peak in breadth is observed as short as 1 year after infection. A high set point viral load seems to be the strongest predictive factor of the quick development of bNAbs. Although it is still unclear how antibodies develop breadth so quickly, these findings provide a proof of concept that, under the right conditions, it is possible to elicit a fast and efficient HIV-neutralizing response.

Goo, L., et al. (2014). Nat. Med. 20, 655–660.

The Right Spot to Integrate and Persist

HIV patients undergoing long-term treatment with combined antiretroviral therapy (cART) frequently show the emergence of identical viruses, suggesting the possibility that the clonal expansion of some HIV-infected cells may play a role in viral persistence. Because HIV has the ability to integrate its DNA into a very large number of sites in the human genome, integration sites can be used as markers of clonally expanded cells. Hughes and colleagues followed five patients chronically infected with HIV to determine the sites of integration of the virus in peripheral blood $CD4^+$ T cells. Before the beginning of cART, all patients present diverse viral populations that converge to identical populations after prolonged cART. The surprises come from the longitudinal analysis of the HIV-infected cells that persist despite the treatment. Though HIV integrates preferentially into actively transcribed genes, persistence is often associated with integration in genes known to be associated with cellular growth and mitosis. These cells clonally expand, and their progeny can be detected for longer than a decade after the initial infection. Similar results are also reported by an independent study by Frenkel and colleagues. They show that the sites of integration do vary between patients and that there is, to some extent, heterogeneity in the insertion sites in different cells from the same patients. Nonetheless, insertions into specific regions such as the

oncogene BACH2 are clearly more frequently observed. Many questions remain. It is unclear whether the selected clonally expanded cells produce infective virions, and therefore it is difficult to estimate their precise contribution for the perpetuation of the chronic infection. Still, these findings strongly suggest that curative HIV therapies will need to block the expansion of the infected cells and unveil the possibility that integration of HIV at specific sites may affect the biology of the cells.
Maldarelli, F., et al. (2014). Science 345, 179–183.
Wagner, T.A., et al. (2014). Science. Published online July 10, 2014. http://dx.doi.org/10.1126/science.1256304.



Stochastic fluctuations in HIV-encoded GFP and mCherry used to identify novel drug synergies. Image courtesy of Leor Weinberger.

Make a Little Noise to Wake Up Dormant Virus

Upon HIV infection, the virus can enter a long-lived proviral latent state during which it is not susceptible to antiretroviral therapy. This latent viral reservoir represents the major obstacle to cure HIV infection. Although small molecules that reactivate the virus by promoting increases in the mean level of HIV gene expression have been identified, thus far they have been unable to efficiently reactivate latency. Leor Weinberger and colleagues hypothesize whether it is possible to improve the efficacy of these drugs using agents that affect ''noise'' or fluctuations around the mean gene-expression level. Indeed, they find that modulating noise in gene expression increases the chances that latent HIV will cross the threshold for latent reactivation. A small-molecule library screen for drugs that modulates noise in gene expression revealed 80 candidates that promote noise but do not change HIV mean expression and therefore would be neglected in conventional screenings. Importantly, these noise-inducing drugs synergize with traditional transcriptional activators, promoting increased HIV reactivation in vitro, with minimal off-target effects in the host cells. Further work will be required to assess the efficacy of this synergy in vivo, but the concept of ''noise screening'' may represent a new general approach to define synergistic drug combinations and manipulate diverse cell-fate decisions.
Dar, R.D., et al. (2014). Science 344, 1392–1396.

There Is a Place and Time for Interferon in HIV Infection

Despite its potent effect in triggering antiviral responses, the role of interferon in HIV infection remains enigmatic. Early reports could not detect beneficial effects of interferon administration to patients chronically infected with HIV, many of whom present high interferon levels even before the beginning of the treatment. Now, Douek and colleagues report that blocking IFN-I receptors in rhesus macaques infected with the simian immunodeficiency virus (SIV) results in faster progression to AIDS. In line with these results, pretreatment of macaques with IFN-α2a limits systemic spread of the virus. Paradoxically, continued treatment with IFN-α2a leads to an ''IFN-desensitized'' state, decreased antiviral gene expression, and increased susceptibility to infection manifested by increased cell-associated virus load and greater depletion of helper T cells. Inflammation and type I interferon production thus might be key in containing the early local infection. However, as the disease progresses and the host becomes desensitized, this balance changes and interferon turns to contribute to immunopathology. The complex temporal dynamic of the innate immune response to retroviruses in primates shows that pro- and anti-inflammatory therapies for HIV need to be approached with caution and must take into account the dual effects of interferon signaling during the course of the infection.
Sandler, N.G., et al (2014). Nature. Published online July 9, 2014. http://dx.doi.org/10.1038/nature13554.

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